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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/519,641

07/15/2005

Bruno Huet De Barochez

SERVIER 437 PCT

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25666 7590 10/29/2008  
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EXAMINER

PALENIK, JEFFREY T

ART UNIT

PAPER NUMBER

1615

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/519,641	HUET DE BAROCHEZ ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 17-32 and 34-37 is/are pending in the application.
- 4a) Of the above claim(s) 27, 29 and 31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-26, 28, 30, 32 and 34-37 is/are rejected.
- 7) ☒ Claim(s) 17 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>22 Dec 2004</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### RESPONSE TO REMARKS

The Examiner thanks the Applicants for their timely reply filed on 21 December 2007, in the matter of 10/519,641.

Cancellation of claim 33 is acknowledged as is the amendment to claim 35 correcting the dependency. Herein, the claims will be reorganized into and considered with Group I (claims 17-32 and 34-36).

Applicants' election **with traverse** of Group I (claims 17-32 and 31-34) is acknowledged. Applicants traverse the lack of unity requirement on the grounds that "the microcapsule composition comprising a perindopril active ingredient is the special technical feature which is defined over the prior art".

Applicants' request for reconsideration of the lack of unity requirement has been fully considered by the Examiner and **is persuasive**. The invention to Meiser et al. (USPN 3,890,442) is art which reads on claim 33. Since claim 33 has been cancelled the art no longer reads on either the method or the composition. Furthermore, in view of the cancellation of claim 33, the remaining claims are deemed by the Examiner to share the same special technical subject matter, thereby justifying the rejoinder of method claim 37 to Group I.

Regarding Applicants' election of the species, the election of perindopril tert-butylamine salt **without traverse** is acknowledged.

The species election results in the withdrawal of claims 27, 29 and 31 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction requirement

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between the compositions and methods.

The remaining claims 17-26, 28, 30, 32 and 34-37 are presented and represent all claims under consideration.

### **INFORMATION DISCLOSURE STATEMENT**

An Information Disclosure Statement (IDS) filed 22 December 2004 is acknowledged and has been reviewed.

### **SPECIFICATION**

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

- (1) if a machine or apparatus, its organization and operation;
- (2) if an article, its method of making;
- (3) if a chemical compound, its identity and use;
- (4) if a mixture, its ingredients;
- (5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

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The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of **50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

**The language should be clear and concise and should not repeat information given in the title.** It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

### CLAIM OBJECTIONS

Claim 1 is objected to because of the following informalities: the term "reservoir" appears in the instant claim in quotes, which indicates to the Examiner that a special definition for the term is implied or intended. However, a search of Applicants' disclosure reveals that no such special definition has been assigned. To avoid confusion, it is suggested that the quotation marks be removed.

Appropriate correction is required.

### CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim

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does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 22 recites the broad recitation "treating a living animal body", and the claim also recites "including a human" which is the narrower statement of the range/limitation. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonably interprets the recited limitation of claim 22 as being a method of administering the claimed composition orally to humans.

### CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-26, 28, 30, 32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garthwaite et al. (US Pre-Grant Publication 2002/0132001) in view of Guez et al. (USPN 6,653,336).

The instant claims are drawn to reservoir microcapsule composition comprising microparticles of the angiotensin control enzyme (ACE) inhibitor perindopril, wherein said microparticles are covered by a film coating comprising a hydrophilic polymer and a hydrophobic polymer, the second of which is present at less than or equal to 40% by weight of the microcapsule, and have a diameter of less than 1200 microns (claims 17 and 23-25). With regard to the limitations recited in claim 23-25, which state that the "coating film enables" a pH-related dissolution profile comprising a latent phase duration of a half hour or longer, and a release phase of perindopril; until some material differences in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward a composition

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of perindopril microcapsules coated with a combination of hydrophilic and hydrophobic polymers, which is instantly claimed. Furthermore, the limitation recited in claim 17, wherein the hydrophobic polymer is present at less than or equal to 40% by weight, is interpreted by the Examiner as including 0% by weight. The hydrophilic polymer is recited as being a copolymer such as methacrylic acid and methyl methacrylate (claims 18 and 19). The hydrophobic polymer is recited as being hydrogenated vegetable oil (claims 20 and 21). Claim 22 recites a ratio range for the hydrophilic and hydrophobic polymers in the coating. Claim 26 recites the elected tert-butylamine salt of perindopril. Claim 28 recites the perindopril active deposited on a neutral core ranging in diameter from 50-600 microns. Composition of the neutral core is recited in claim 30. Claim 32 recites the composition of claim 17 further comprising indapamide microcapsules. Independent claim 34 recites a pharmaceutical composition comprising the perindopril microcapsules of claim 17 and further comprising at least one pharmaceutically acceptable excipient. Dosage forms for the composition of claim 34 are recited (claims 35 and 36). Independent claim 37 recites a method of treating arterial hypertension comprising administering the composition of claim 17 to an animal such as a human.

Garthwaite et al. teach a composition comprising dual antihypertensive agents wherein the first of said agents is taught as eplerenone and the second of which is taught as preferably being a different antihypertensive agent such as a diuretic or an ACE inhibitor (claims 1, 9, 10 and 14). Perindopril is an example of an ACE inhibitor and indapamide is an example of a diuretic, both of which are taught in the Table in ¶[0087]. The same table also teaches eplerenone as an example of a diuretic compound. The composition is further taught as a capsule comprising enterically coated pellets (claim 17). Said pellets are taught as having a preferred core formulation comprising



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cellulose or cellulose derived material ¶[0132] and more preferably lactose or microcrystalline cellulose ¶[0133]. The uncoated cores are taught as being in the form of generally spherical beads having a diameter of 1,000 microns or less and preferably ranging from about 200-800 microns ¶[0141]. In the case of the coated, active-loaded core, typical diameters, particularly in the case of pellets or beads, ranges from 200 to 1700 microns ¶[0140]. Enteric coatings on the cores are taught as being used to control the release of the antihypertensive formulations contained therein ¶[0146]. The coating is taught as being produced from copolymers of acrylic acid and methacrylic acid or esters of either monomer, which are referred to overall as “polymerized acrylates” ¶[0147]. Specific examples of polymerized acrylates include Eudragit® L and Eudragit® S, the commercial brand names for methacrylic acid/methyl methacrylate copolymer (see *Degussa Specifications and Test Methods*). In addition to the polymers, the coating layer typically includes a lubricant such as hydrogenated vegetable oils ¶¶[0155], [0124] and [0125]. The polymeric coating is taught as comprising about 10-50% by weight of polymerized acrylates ¶[0148] and the lubricants, if present, are taught as ranging between 0.1-10% by weight ¶[0126]. Mixed together in the enteric coating, a ratio of polymerized acrylates to lubricant is established, such as 10%:10% or 1:1. Additional excipients are taught such as diluents, disintegrants, binding agents and wetting agents are taught ¶¶[0106] – [0123]. Dosage formulations such as tablets and hard gelatin capsules are taught by Examples 1-3 and 4-7, respectively. Claims 19-21 teach orally administering the composition discussed above as a means for treating humans for elevated blood pressure.

Garthwaite et al. do not expressly teach the microcapsules as comprising the elected tert-butylamine salt of perindopril or the claimed combination of said salt microcapsules with indapamide microcapsules.

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Guez et al. teach orally administering a combination dosage comprising an ACE inhibitor and diuretic for the treatment of arteriolo-capillary microcirculatory disorders such as arterial hypertension (Abstract, col. 3, lines 1-10). The preferred combination of ACE inhibitor and diuretic is further taught as being Perindopril tert-butylamine salt and Indapamide, respectively (col. 3, lines 33-38). Examples 1 and 2, in particular, teach tablet formulations comprising Perindopril tert-butylamine salt and Indapamide in combination with hydrophobic polymeric lubricants such as magnesium stearate and hydrophilic polymeric cellulose compounds such as microcrystalline cellulose. Example 19 further teaches the preferred Perindopril salt-Indapamide combination as being significantly pertinent to decreasing arterial pressure (col. 7, lines 48-49). Though tablets are taught as the preferred form of oral administration, other routes such as capsules, including hard gelatin capsules are also taught (col. 3, lines 39-50).

Guez et al. do not expressly teach the two preferred active ingredients in the form of microencapsulated pellets or granules nor are the two actives expressly taught as being encapsulated separate from one another but within the same dosage form.

In view of the combined teachings of the prior art, it would have been obvious to one of ordinary skill in the art, at the time of the invention, to prepare a composition comprising hydrophilic/hydrophobic polymer encapsulated perindopril and indapamide microparticles, as taught and suggested by Garthwaite and Guez, modify the ratio of the coating ingredients, and produce the instant invention.

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One of ordinary skill in the art would have been motivated to do this because Garthwaite teaches enterically coated particles comprising a first anti-hypertensive agent, specifically a diuretic, and an additional anti-hypertensive agent, such as an ACE inhibitor. The Table in ¶[0087], as discussed above, teaches the ACE inhibitor perindopril as well as the diuretic indapamide. The motivation for the skilled artisan to substitute a thiazide diuretic such as indapamide for a potassium-sparing diuretic such as eplerenone, is based on two points: (1) that despite their chemical distinction, both compounds target the renal system to accomplish the same fundamental end, namely increased excretion of water from the body, and (2) they share at least one chemical pathway by which said elevated water excretion is achieved, namely preventing the reabsorption of sodium and chloride ions (see *The Drug Monitor*). The skilled artisan would have been further motivated to combine indapamide specifically with the tert-butylamine salt of perindopril not only because Garthwaite and Guez teach overlapping technology, namely establishing tablet and/or gelatin capsule dosage forms comprising both active agents admixed with hydrophilic and hydrophobic polymeric additives, but more importantly because Guez expressly teaches the combination of actives as being effective at alleviating arterial hypertension or pressure (see Example 19 of Guez).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the combined references, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

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**CORRESPONDENCE**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/  
Examiner, Art Unit 1615

/MP WOODWARD/  
Supervisory Patent Examiner, Art Unit 1615